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10/045,178	01/11/2002	Noriyuki Kasahara	0072601-000005	7589

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/045,178	KASAHARA ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-46,49-51,56,58,59,61,63-73,75,78-82 and 87-121* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-45,49-51,56,58,59,61,63-73,75,78-82 and 87-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

2. Claims 1-40, 47, 48, 52-55, 57, 60, 62, 74, 76, 77, and 83-86 have been cancelled. Claim 46 has been withdrawn. Claims 41, 56, 61, 66, 75, 80-82, and 87-96 have been amended. Claims 97-121 are new.

Claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, 87-121 are under examination.

3. All rejections pertaining to claim 77 are moot because Applicant cancelled the claim in the response filed on 10/31/2007.

Withdrawn Rejections/Objections

4. The following rejections/objections are withdrawn in response to Applicant's arguments filed on 10/31/2007:

The objection to claim 51 under 37 CFR 1.75(c) as being in improper form because it is dependent from claim 64;

The rejection of claims 41-44, 49-5156, 58, 59, 61, 63-73, 75, 78-82, and 87-96 under 35 U.S.C. 112, first paragraph.

The following rejections are withdrawn in response to Applicant's amendments to the claims filed on 10/31/2007:

The rejection of claims 41-45, 49-51, 56, 61, 66, 70, 71, 73, 75, 78-80, 87, 89, and 91 under 35 U.S.C. 103(a) as being unpatentable over Ram et al. (Cancer Research, 1993, 53: 83-88), in view of both Martuza (Nature Medicine, 1997, 3: 1323) and Martuza et al. (U.S. patent No. 5,585,096);

The rejection of claims 41-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 78-80, 87-92 under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with Martuza and Martuza et al., in further view of both Kuryama et al. (Int J Cancer, 1997, 71: 470-475) and Yan et al. (Prostrate, 1997, 32: 129-139);

The rejection of claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 78-80, 81, 82, 87, 89-91, 93, and 95 under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with Martuza and Martuza et al. (the '096' patent), in further view of Kasahara et al. (Science, 1994, 266: 1373-1376);

The rejections of claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 78-80, 81, 82, 87, 89-91, and 93-96 under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with Martuza, Martuza et al. (the '096' patent), and Kasahara et al., in further view of Kuryama et al.

New Rejections

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, 87-121 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-16, 19, 22, 23, 25, and 26 of copending Application No. 11/805,411 in view of both Yan et al. (Prostrate, 1997, 32: 129-139, of record) and Sobol et al. (U.S. patent No. 5,674,486).

This is a provisional obviousness-type double patenting rejection.

The instant claims are drawn to a method of treating a human subject having a cell proliferative disorder by *in vivo* administering to the subject a recombinant

replication competent oncoretroviral polynucleotide or a recombinant replication competent oncoretrovirus, wherein the polynucleotide or virus comprise polynucleotides encoding GAG, POL and envelope (ENV), an oncoretroviral polynucleotide comprising LTRs at the 5' or 3' its ends, a cassette having an IRES operably linked to a heterologous nucleic acid encoding a suicide gene or a cytokine, wherein the cassette is inserted 5' to the 3' LTR and 3' to the polynucleotide encoding ENV and wherein the recombinant replication competent oncoretroviral polynucleotide also comprises cis-acting nucleic acid sequences for reverse transcription, packaging, and integration in a target cells; the expression of the suicide gene is activated by administering a pro-drug and the cytokine could be IL-1 to IL-12 or IFNγ (claims 41-45, 61, 66, 67-69, 78, 81, 82, 87, 95, 97-101, 103-105, 107, 109, 111, 113, 116-119, and 121). The proliferative disorder could be melanoma or glioblastoma (claims 56, 75, 87, 89, 91, 93, and 95), the LTR comprises a tissue specific promoter such as the probasin promoter (claims 58, 59, 88, 90, 92, 94, 96, 106, 108, 110, 112, 114), the ENV is amphotropic or ecotropic (claims 50 and 72) or a chimeric protein comprising a targeting ligand such as an antibody (claims 63-65, 81, 82, 93, 95, 103, 104, 111, and 113) or a non-retroviral envelope (claims 119 and 120). The GAG, POL and ENV are from MoMLV wherein the MoMLV can be amphotropic or ecotropic (claims 49-51, 70, 71, 80, 91, 102, 109, 115-120). With respect to claims 49-51, 70, 80, 91, 102, 109 and 115 it is noted that they recite GAG, POL and ENV from MLV and not MoMLV. However, MLV is not a species but rather a genus comprising several species of murine leukemia viruses among which is Moloney murine leukemia virus (MoMLV). Because the claims do not specifically

recite an MLV species and because the only MLV species envisioned by the instant specification is MoMLV, claims 49-51, 70, 80, 91, 102, 109 and 115 are interpreted as being drawn to MoMLV.

The application claims recite a method of treating a human patient by *in vivo* transfecting a cell in the patient with a plasmid encoding a replication-competent retrovirus (i.e., a recombinant replication competent oncoretroviral polynucleotide), wherein the replication-competent retrovirus comprises sequences encoding GAG, POL, ENV, LTR, a heterologous coding sequence encoding a therapeutic protein operably linked to a regulatory nucleic acid sequence, and one or more targeting sequences for cell- or tissue-specific targeting operably linked to the sequence encoding the therapeutic protein (claims 13, 14, 19, 25, and 26). The condition to be treated is a cell proliferative disease, wherein the cell proliferative disorder could be cancer (claims 15 and 16), the tropism of the retrovirus is altered (claim 22) and the plasmid is introduced by hydrodynamic transfection (claim 23). The specification defines the recombinant replication competent oncoretroviral polynucleotide is from MoMLV (i.e., GAG, POL and ENV are derived from MoMLV), that ENV can be amphotropic or ecotropic, and that the heterologous sequence encoding the therapeutic protein is operably linked to the regulatory nucleic acid sequence via an IRES, wherein the IRES and the heterogeneous gene form a cassette which is located 5' to the 3' LTR and 3' to the sequence encoding ENV (p. 1, paragraph 0017, p. 8, paragraph 0117, Fig. 1). The specification also discloses that the heterologous therapeutic sequence is a cytokine (such as interleukins) or a suicide gene which activates a prodrug, the plasmid

contains sequences required for the production of virus within the transfected cell (i.e., cis-acting nucleic acid sequences for reverse transcription, packaging, and integration in a target cells), the tropism of the virus is altered by using a chimeric protein ENV-antibody or a non-retroviral envelope such as that of VSV or CMV, the targeting sequences for cell- or tissue-specific targeting of the retrovirus is a tissue-specific promoter linked to the 5' and/or 3' LTR to create a chimeric LTR (p. 4, paragraphs 0054, 0058-0061 and 0064, p. 5, paragraph 0067, p. 8, paragraphs 0114, 0116, 0117, and 0119). With respect to the limitation of treatment by using a recombinant replication competent oncoretrovirus (instant claims 41-45, 49-51, 56, 58, 59, 61, 63-65, 78, 80, 81, 87, 88, and 91-94), it is noted that the administration of the plasmid to a patient, as recited in the application claims, would necessarily result in the *in vivo* production of the virus; therefore, by reciting treating via administering a plasmid, the claims of the Application No. 11/805,411 embrace a method of treatment by using a recombinant replication competent oncoretrovirus. With respect to the limitations of treating melanoma or glioblastoma, one of skill in the art would have known to use the recombinant retrovirus of the Application No. 11/805,411 to treat these forms of cancers because claim 16 discloses that the virus can be used to treat any cancer type. The application claims do not disclose the probasin promoter. However, at the time of filing the probasin promoter was known and used in the prior art, for example the probasin promoter was used by Yan et al. to target gene expression in the prostrate (Abstract, p. 130, columns 1 and 2, p. 133, column 2). Therefore, one of skill in the art would have known to use the probasin promoter to specifically target the suicide genes to prostrate

tumors for increased treatment efficiency of such tumors. With respect to the limitations recited in the instant claims 116-118, it is noted that the art teaches cancer therapy by using a variety of cytokine, including IFNγ (see Sobol, Abstract, column 4, lines 25-27). It would have been obvious to one of skill in the art, at the time the invention was made to use a gene encoding IFNγ to achieve the predictable result of treating cancer.

Thus, the application claims 13-16, 19, 22, 23, 25, and 26 of copending Application No. 11/805,411 embrace all limitations of the instant claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, 87-121. Therefore, the application claims and the instant claims are obvious variants of one another.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 41-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. (Cancer Research, 1993, 53: 83-88, of record), in view of each Martuza et al. (U.S. Patent No. 5,585,096, of record), Murakami et al. (Gene, 1997, 202: 23-29), and Sobol et al. (U.S. patent No. 5, 674,486).

** Claims 49-51, 70, 80, 91, 102, 109 and 115 recite GAG, POL and ENV from MLV and not MoMLV. However, MLV is not a species but rather a genus comprising several species of murine leukemia viruses among which is Moloney murine leukemia virus (MoMLV). Because the claims do not specifically recite an MLV species and because the only MLV species envisioned by the instant specification is MoMLV, claims 49-51, 70, 80, 91, 102, 109 and 115 are interpreted as being drawn to MoMLV.

Ram et al. teach a method of treating glioblastoma (i.e., a cell proliferative disorder) in rats by the *in vivo* intratumoral administration of a therapeutically effective amount of cells producing a retrovirus comprising 5' and 3' long terminal repeats (LTR) and a heterologous nucleic acid sequence encoding the HSV thymidine kinase (tk) (i.e., a suicide gene) that uses the 5' LTR as its promoter (i.e., operably linked to a regulatory nucleic acid sequence), followed by contacting the rats with ganciclovir (i.e., a prodrug), wherein the ganciclovir is activated by the tk expression; since the cells are administered to the animal, they must necessarily be administered in a pharmaceutically acceptable carrier (i.e., the retrovirus is contained in a pharmaceutically acceptable carrier) (claims 41, 42, 44, 45, 66, 78, 79, 87, 89, 97, 100, 105, 107, 119, and 121) (Abstract, p. 83, columns 1 and 2, p. 84, column 1, p. 85, column 2). Ram et al. teach that the retroviral vector is MoMLV, i.e., a mammalian oncoretrovirus (claims 49, 61, 70, 80, 91, 99, 102, 109, and 115) (p. 83, column 1). Ram et al. teach their approach as suitable for the treatment of localized tumors in humans (claim 43) (Abstract, p. 83, column 2, second full paragraph, p. 88, column 1).

Ram et al. teach administering cells producing replication deficient MoMLV and not a replication competent retrovirus, as recited by the instant claims 41, 66, 80, 87, 89, 91, 97, 100, 102, 105, 107, 109, 119, and 121. However, at the time of filing, the advantages of using replication competent retroviruses for cancer treatment was taught by the prior art. For example, Martuza et al. teach that the administration of replication deficient viruses or of cells producing replication deficient viruses is not applicable to the treatment of tumors in humans because, since the virus cannot replicate, gene transfer occurs within a few cell-distances, which leads to inefficient gene delivery; for theses reasons, Martuza et al. suggest the use of replication competent viral vectors (column 2, lines 1-45, column 5, lines 14-18). Martuza et al. teach that such replication competent retroviruses can be used to treat melanoma (claims 56, 75, 98, and 101) (column 3, lines 52-55). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. by using a replication competent MoMLV (i.e., an oncoretrovirus comprising MoMLV GAG, POL, ENV, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration into a target cell), with a reasonable expectation of success. The motivation to do so is provided by Martuza et al., who teach the necessity to replace replication deficient viruses with replication competent viruses for efficient gene therapy in animals and humans. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that replication competent viruses can be successfully obtained and used for cancer treatment. With respect to the limitation of the MoMLV being an amphotropic MoMLV (claims 50 and 71), since the

teachings of Ram et al. and Martuza et al. (U.S. Patent No. 5,585,096) disclose MoMLV suitable for therapy in humans, their MoMLV must necessarily be amphotropic (i.e., allows transduction of cells of other species than the mouse).

Ram et al. and Martuza et al. do not teach a cassette comprising an internal ribosome entry site (IRES) operably linked to the suicide gene, wherein the cassette is located 5' to the 3' LTR and 3' to the sequence encoding ENV (claims 41, 66, 80, 87, 89, 91, 97, 100, 102, 105, 107, 109, 119, and 121). However, at the time of filing the use of cassettes comprising IRES operably linked to heterologous genes was known in the prior art, for example Murakami et al. teach insertions of such cassettes into retroviral vectors, wherein the cassettes are inserted 5' to the 3' LTR and 3' to the sequence encoding ENV (p. 25, Fig. 1A). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. and Martuza et al. by inserting an IRES-suicide gene cassette in their MoMLV, as taught by Murakami et al., with a reasonable expectation of success. The motivation to do so is provided by Martuza et al. who teach that introduction of such IRES cassettes 5' to the 3' LTR and 3' to the sequence encoding ENV results in increased expression of heterologous genes as compared to the vectors lacking the IRES cassettes (Abstract, p. 23, column 2, last paragraph, p. 28, column 2, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murakami et al. teach that IRES cassettes can be successfully inserted into retroviral vectors.

With respect to the limitation of a viral vector encoding a cytokine (claims 97, 100, 102, 105, 107, 109, and 119), Martuza et al. teach tumor killing by using replication competent viruses lacking a suicide gene and comprising a gene encoding a cytokine, wherein tumor killing is enhanced by cytokine expression in the tumor (column 11, lines 35-55). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made to substitute the suicide gene with a gene encoding a cytokine to achieve the predictable result of killing tumor cells. With respect to the limitations recited in claims 116-118, it is noted that the art teaches cancer therapy by using a variety of cytokine, including IFNγ (see Sobol, Abstract, column 4, lines 25-27). It would have been obvious to one of skill in the art, at the time the invention was made to use a gene encoding IFNγ to achieve the predictable result of treating cancer.

With respect to the limitation of treatment by using a recombinant replication competent oncoretrovirus (instant claims 41, 80, 81, 87, 91, 93, 97, 102, 103, 105, 109, and 119), it is noted that the administration of the replication competent MoMLV to a patient would necessarily result in the *in vivo* production of the virus, and therefore, the combined teachings above embrace a method of treatment by using a recombinant replication competent MoMLV.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they apply to the instant rejection:

Applicant argues that the cited portions of Ram et al. describe a method that utilizes "retroviral producer cells" injected at the site of a tumor (p. 86, column 2, last paragraph), wherein the producer cells support the in situ production of a retroviral vector containing a suicide gene and wherein the producer cells are necessary because the vector is not replication competent. Further, Applicant argues, the nucleic acid sequence encoding the suicide gene is located "just downstream of the 5' long terminal repeat sequence" (p. 84, column 1, lines 2-4). Therefore, Applicant submits that the cited portions of Ram et al. fail to describe a replication competent oncoretrovirus in the absence of a producer cell to achieve efficient transduction and that the cited portions of Ram et al. also fail to appreciate the desirability of positioning a nucleic acid sequence encoding a therapeutic polypeptide in a non-LTR region of the viral vector. With respect to Martuza et al./Ileana Popa/

Primary Examiner, Art Unit 1633, Applicant argues that, although they describe competent viral vectors derived from adenovirus and herpes simplex virus, they fail to remedy the deficiencies of Ram et al. because, like Ram et al., they fail to appreciate the importance of positioning a cassette that includes an IRES sequence operably associated with a heterologous sequence 5' to the 3' LTR and 3' to the envelope gene of the viral vector. Applicant also argues that one of skill in the art would not have known how to modify a retrovirus (i.e., an RNA virus) in order to make it replication competent as claimed because Martuza et al. describe adenoviruses and herpesviruses, which are DNA viruses. Therefore, Applicant asserts that one of skill in the art would not have known how to make an RNA virus replication competent based

on a disclosure of how to make a DNA virus replication competent as their genomes are completely different. In contrast, Applicants argues, the instant invention is drawn to a replication competent oncoretroviral vector with an enhanced capability to stably deliver a heterologous sequence to a dividing cell; once integrated into a target cell, the vector produces a therapeutic polypeptide encoded by the heterologous sequence and viral particles which infect neighboring dividing cells are also produced. Applicant submits that in cases involving methods of treatment utilizing replication competent retroviruses, it remains necessary to identify some reason that would have led the skilled artisan to combine known retroviral components in a particular manner, and in a particular sequence, to establish a *prima facie* case of obviousness. Applicant asserts that the cited references, in combination, fail to describe utilizing a replication competent oncoretrovirus as described in the present application in a manner that achieves the claimed methods; specifically, they fail to provide a reasonable expectation that the combination of viral components would result in a replication competent oncoretrovirus useful for treating cell proliferative disorders. Therefore, Applicant argues that the claims are not obvious over the cited art and requests withdrawal of this rejection.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). While it is true that Ram et al. administering cells producing MoMLV and not replication competent retroviruses, the prior art teaches the advantages of administering replication competent viruses and not producer cells because they are able to enter into tumor cells, make copies, lyse the cell and spread to the neighboring tumor cells; in contrast, the use of producer cells is not adequate for treating tumors in humans because the cells produce replication defective viruses which cannot replicate, and therefore, gene transfer occurs within a few cell-distances from the producer cells which leads to inefficient gene delivery (see Martuza et al. above). Based on these teachings, one of skill in the art would have been motivated to modify the method of Ram et al. by replacing the MoMLV producer cells with a replication competent MoMLV. The argument that one of skill in the art would not have been expected to have a reasonable expectation of success in extrapolating the teachings from DNA viruses to RNA viruses is not found persuasive because Applicant did not provide any evidence to support this argument. In fact, making replication competent retroviral vectors including replication competent MoMLV was routine in the art at the time the invention was made (Vile et al., Virology, 1995, 214: 307-313, see the entire paper) and therefore, one of skill in the art would have expected to successfully obtain a replication competent MoMLV. Similarly, Applicant's argument that, as opposed to the instant invention, Ram et al. teach inserting the suicide gene downstream to the 5' LTR and that the prior art provides no motivation to insert the suicide gene as claimed (i.e., as part of an IRES cassette, wherein the IRES cassette is inserted 5' to the 3' LTR and 3' to the sequence encoding ENV) is not supported by evidence. As noted above, Murakami et al. teach insertions of

IRES cassettes into retroviral vectors, wherein the cassettes are inserted 5' to the 3' LTR and 3' to the sequence encoding ENV and wherein the use of such retroviral vectors results in increased expression of heterologous genes as compared to the vectors lacking the IRES cassettes. Therefore, Applicant's argument of lack of motivation is not found persuasive because, based on the teachings in the prior art, one of skill in the art would have been motivated to insert an IRES-suicide gene cassette 5' to the 3' LTR and 3' to the sequence encoding ENV in order to obtain higher suicide gene expression. It is noted that by combining the teachings of the references cited above, one of skill in the art would have necessarily obtained the claimed vector, i.e., a replication competent oncoretroviral vector with enhanced capability to stably deliver a heterologous sequence to a dividing cell. For these reasons, the rejection is maintained.

9. Claims 41-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of Douar et al. (Gene Ther, 1996, 3: 789-796, Abstract).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach a non-retroviral envelope, such as that of VSV (claims 119 and 120). Douar et al. teach VSV-G pseudotyped MoMLV (Abstract). It would have been

obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by using a VSV-G pseudotyped MoMLV, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Douar et al. teach that VSV-G pseudotyped MoMLV has a broader host range. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that VSV-G pseudotyped MoMLV can be successfully obtained and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. Claims 41-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 78-80, 87-92, 97-102, 105-110, 115-119, and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of both Vile et al. (Virology, 1995, 214: 307-313) and Yan et al. (Prostrate, 1997, 32: 129-139, of record).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 106, 108, and 110). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column 1). It would

have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted (Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Vile et al. do not teach the probasin promoter (claim 59). However, at the time of filing the probasin promoter was known and used in the prior art, for example the probasin promoter was used by Yan et al. to target gene expression in the prostrate (Abstract, p. 130, columns 1 and 2, p. 133, column 2). Therefore, one of skill in the art would have known to use the probasin promoter to specifically target the suicide genes to prostrate tumors for increased treatment efficiency of such tumors.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they apply to the instant rejection:

Applicant argues that Yan et al. do not cure the deficiencies of Ram et al. and Martuza et al. Applicant's argument is acknowledged, however, the argument is not found persuasive for the reasons set forth above.

11. Claims 41-45, 49-51, 56, 58, 61, 63-73, 75, 78-82, 87-119, and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of both Kasahara et al. (Science, 1994, 266: 1373-1376, of record) and Vile et al.

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza, Martuza et al., Murakami et al., and Sobol et al. do not teach a chimeric envelope, wherein the chimeric protein comprises a targeting ligand such as a receptor ligand (claims 63-65, 67-69, 73, 81, 82, 93, 95, 103, 104, 111, and 113) or an ecotropic envelope (claim 72). Kasahara et al. teach tissue specific targeting of MoMLV retroviral vectors to cells expressing the erythropoietin (EPO) receptor by engineering the vector to encode a chimeric ecotropic MoMLV protein, wherein the chimeric envelope protein comprises EPO (p. 1373, column 2, p. 1374, column 3 bridging p.1375). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by engineering their vector to encode

an ecotropic envelope fused to a receptor ligand, with a reasonable expectation of success. The motivation to do so is provided by Kasahara et al., who teach that such viruses can be used to specifically infect human cells expressing the receptor for the ligand and that such a strategy can be used for the treatment of cancer (p. 1373, column 1, p. 1375, column 1 bridging column 2, and column 3). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that such engineered retroviruses can be successfully made and used.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 94, 96, 106, 108, 110, 112, and 114). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al., by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted

(Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they apply to the instant rejection:

Applicant argues that Kasahara et al. do not cure the deficiencies of Ram et al. and Martuza et al. Applicant's argument is acknowledged, however, the argument is not found persuasive for the reasons set forth above.

Claim Rejections - 35 USC § 112, new matter

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, 87-121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claims to include the recitation that the retroviral polynucleotide comprises LTRs "at the 5' or 3'" ends is considered new matter.

Applicant points to paragraphs 0004 and 0099 of PGPUB 2002/0127697 for support. It is noted that the indicated passage does provide support for such a limitation. A search of the remaining portions of the specification failed to provide literal or figurative support for LTR et either 5' or 3' end, in the alternative. The specification only provides support for a retroviral polynucleotide comprising LTRs at both 5' and 3' ends. Moreover, it is noted that a retroviral vector with only one LTR at one end could not function in the claimed invention.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often

necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

14. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Ileana Popa/

Art Unit 1633